

## Is misoprostol teratogenic?

### *Misoprostol use during early pregnancy and its association with Möbius' syndrome*

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Pastuszek A, Schuler L, Speck-Martins CE, Coelho KA, Cordelo SM, Vargas F, et al. Use of misoprostol during pregnancy and Möbius' syndrome in infants. *N Engl J Med* 1998; 338:1881-5.

#### Research question

Is there an association between unsuccessful abortifacient use of misoprostol during the first trimester of pregnancy and Möbius' syndrome (congenital facial paralysis) in infants?

#### Type of article and design

Retrospective case-control study.

#### Relevance to family physicians

Misoprostol, a synthetic prostaglandin E<sub>1</sub>, is commonly used to prevent and treat nonsteroidal anti-inflammatory drug-induced gastritis and peptic ulcer disease. It can also stimulate uterine contractions and cause vaginal bleeding. When used in combination with methotrexate, it is considered effective for nonsurgical abortions.<sup>1</sup> Misoprostol is not recommended as a lone abortifacient, however, due to its low efficacy.

Recently a young woman who was 26 weeks pregnant visited the community health centre in distress and revealed that she had attempted to abort her pregnancy. On the advice of a friend, she had taken three tablets of misoprostol (600mg) orally during her first trimester. She experienced cramping and 3 days of vaginal bleeding, and assumed she had aborted her fetus. Two months passed before she realized her pregnancy continued and sought medical care. We consulted the Motherisk Program, and they confirmed a fetal risk: an association with Möbius' syndrome. They also confirmed that this abortion attempt was not an isolated incident in Canada.

Möbius' syndrome consists of congenital facial nerve paralysis with or without paralysis of other cranial nerves and deformities of

the limbs.<sup>2</sup> Pathogenesis is believed to be due to disrupted blood flow during early embryonic development. Failed abortion, prolonged rupture of membranes, and chorionic-villus sampling have been implicated. Misoprostol might also increase the risk of such a scenario.

#### Overview of study and outcomes

This case-control study was conducted in Brazil by the Motherisk Program at the Hospital for Sick Children in Toronto, Ont. Elective abortions are prohibited in Brazil, and many women who attempt abortion use misoprostol, which is available over the counter. Up to 80% of these pregnancies, however, continue to term.

The study compared 96 infants with Möbius' syndrome (cases) with 96 infants with neural tube defects (controls). Möbius' syndrome was defined as bilateral or unilateral facial nerve paralysis with or without other neurologic signs or malformations. Infants born with neural tube defects during the same period (1990 to 1996) were selected from the rosters of the same clinical geneticists.

At the time of each diagnosis, the geneticists had interviewed the mothers and recorded information about the pregnancies in the mothers' records. Information was extracted from the records using a standardized form (translated from Portuguese to English) and sent to Toronto for analysis.

#### Results

Almost half (49%) the mothers of infants with Möbius' syndrome had used misoprostol during the first trimester compared with 3% of mothers of infants with neural tube defects (odds ratio [OR] 29.7; 95% confidence interval [CI] 11.6 to 76.0). Several of the mothers (20/47) had taken misoprostol orally; 20 had used it both orally and vaginally. Mean dose of misoprostol used was 842 µg (±543 µg).

Comparison of baseline characteristics showed that mothers

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of infants with neural tube defects were older. More infants with neural tube defects had low birth weights (<2500 g) and were more likely to have been delivered by cesarean section. The two groups were statistically similar in educational level, gravidity, parity, number of previous miscarriages and induced abortions, rate of consanguinity, cigarette and alcohol use, and presence or absence of hyperthermia in the first trimester.

### Analysis of methodology

In this case-control study, the authors identify and clearly discuss several potential biases: differential maternal recall bias, underascertainment of misoprostol use in controls, and overreporting of Möbius' syndrome. They identify the direction of bias and conservatively re-analyze the data. Results remain significant (OR 8.2; 95% CI 4.1 to 16.8). That 3% of women in the control group were exposed to misoprostol was considered similar to exposure of mothers delivering normal infants in Brazil.

The main weakness from a Canadian perspective is the study population. Brazilians have different environmental exposures than Canadians have. Also, the exact timing and dose of misoprostol were difficult to ascertain, and this adds a degree of uncertainty to the association.

In a recent Motherisk prospective cohort study,<sup>3</sup> 86 women exposed to misoprostol were compared with matched controls in Brazil. Results failed to demonstrate a significant difference in major and minor birth defects between the two groups. There were, however, significantly more miscarriages in the exposed group (18.3% versus 5.8%, relative risk 3.15, CI 1.2 to 8.3). Möbius' syndrome is rare. In rare disorders, an OR in a well-designed study can be considered an estimate of relative risk, but it is not equivalent to the "gold standard" relative risk from a prospective cohort study.

### Application to clinical practice

Results of this well-conducted study suggest a strong association between misoprostol and Möbius' syndrome. Physicians should be aware of this potential teratogenicity as well as the established risk of miscarriage.

Two common clinical scenarios give rise to these risks. The first is described in this study, that of a woman self-medicating to produce abortion. The second is any indication for a cytoprotective nonsteroidal anti-inflammatory drug in women of childbearing age. The second scenario includes myriad strains, sprains, and pains, making it quite common in primary care.

Pastuszak et al do not address the cytoprotective use of misoprostol. The mean dose used by subjects in their study, however, is comparable to the total

recommended daily dose of misoprostol (800 µg/d) in Canada.<sup>4</sup> In a recent Canadian review article, Bensen and Zizzo<sup>5</sup> discuss using nonsteroidal anti-inflammatory drugs in combination with misoprostol to improve gastrointestinal safety. When using misoprostol, however, physicians should ensure effective birth control.

Nonsurgical abortions using misoprostol in combination with methotrexate, are increasing in Canadian clinical practice. As the general public becomes aware of this practice, there is a greater risk for unsupervised abortifacient use of misoprostol. Family physicians should be aware of these abortion techniques and the need for medical follow up.

Möbius' syndrome is rare. Estimates are controversial because of recent refinements in diagnostic criteria and because the syndrome is not routinely included in birth defect surveillance. Möbius' syndrome has an incidence of 1/10000 to 1/50000 live births estimated from cases reported in the literature (personal communication from L. Schuler 1998, Oct 20). Even with this low incidence, the high OR associated with misoprostol could increase the baseline risk to nearly 1%, which is clinically significant.

### Bottom line

This high OR suggests a strong association between unsupervised unsuccessful use of misoprostol for attempted abortion and Möbius' syndrome. Case-control methodology has inherent limitations; however, this could be the best evidence available. Misoprostol, commonly used in primary care:

- is contraindicated in pregnancy,
- carries a teratogenic risk for Möbius' syndrome, and
- has been used without supervision by women attempting to terminate their pregnancies.

When treating soft tissue inflammation, we should think twice before prescribing misoprostol to women of childbearing age. ♦

### References

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